

Page 52, after line 2 add at the margin - Ciliberto, G., Albrecht, U., Sterrer, S., and Risau, W., Developmental Biology, 1983 18 59-88-; and

after line 18, add at the margin - Hitt, M., Bret, A. J., Prevec, L. and Graham, F. L. Cell Biology: A Laboratory Handbook, J. Celis (ed), Academic Press N.Y. 1994-.

After page 53, add the Sequence Listing section attached to this Amendment.

IN THE CLAIMS

Cancelled
Please amend the claims of the original application (which have now been deleted) as follows.

1. *See and a* (Amended) A composition comprising a nucleic acid sequence and a hyaluronic acid or a derivative thereof, together with a pharmaceutically-acceptable carrier, wherein the nucleic acid is either an anti-sense nucleic acid directed against a target sequence or a sense nucleic acid encoding a desired protein.
2. A composition according to Claim 1, in which the nucleic acid is a nucleotide sequence which is in the anti-sense orientation to a target sequence.
3. A composition according to Claim 2, in which the target nucleic acid sequence is a genomic DNA, a cDNA, a messenger RNA or an oligonucleotide.
4. A composition according to Claim 1, in which the nucleic acid is present in a vector comprising a nucleic acid sequence to be transferred into a target cell.
5. A composition according to Claim 4, in which the nucleic acid sequence to be transferred is a genomic DNA, a cDNA, a messenger RNA or an oligonucleotide.
6. A composition according to Claim 5, wherein the vector comprises a sense sequence to be provided to a target cell in order to exert a function.
7. A composition according to Claim 6, in which the vector comprises an anti-sense sequence to be provided to a target cell in order to inhibit the functioning of a nucleic acid present in the target cell.
8. A composition according to any one of Claims 1 to 7, in which the vector is a liposome.
9. A composition according to any one of Claims 1 to 8, in which the vector is a virus.
10. A composition according to any one of Claims 1 to 9, in which the virus is an adenovirus, an adeno-associated virus, a herpes virus or a retrovirus.
11. A composition according to Claim 9, in which the virus is a replication-

defective adenovirus.

12. A composition according to Claim 11, where the virus is a replication-defective adenovirus comprising a promoter selected from the group consisting of respiratory syncytial virus promoter, cytomegalovirus promoter, adenovirus major late protein (MLP), VA1 pol III and b-actin promoters.

13. A composition according to Claim 11, wherein the vector is pAd.RSV, pAd.MLP or pAd.VA1.

14. A composition according to Claim 11, wherein the vector is Ad.RSV.aVEGF or Ad.VA1.aVEGF.

15. A composition according to any one of Claims 10 to 14, wherein the vector also comprises a polyadenylation signal sequence.

16. A composition according to Claim 15, wherein the polyadenylation signal sequence is the SV40 signal sequence.

17. A method of treatment of a pathological condition in a subject in need of such treatment, comprising the step of administering an effective dose of a composition according to any one of Claims 1 to 16 to said subject.

18. A method according to Claim 17, in which the composition is administered systemically by injection.

19. A method according to Claim 17, in which the composition is administered topically.

20. A method according to Claim 17, in which the composition is administered directly into the tissue to be treated.

21. A method of preparing a composition according to any one of Claims 1 to 16, comprising the step of binding a nucleic acid or vector to a hyaluronic acid or a derivative thereof, and isolating the thus-formed complex.

22. A composition for treatment of a retinal disease mediated by abnormal vascularization comprising

a) an anti-sense nucleic acid sequence directed against vascular endothelial growth factor (VEGF), and

b) hyaluronic acid,

together with a pharmaceutically-acceptable carrier.

23. A composition according to Claim 22, in which the anti-sense nucleic acid sequence is present in a vector comprising a nucleic acid sequence to be transferred into a

target cell.

24. A composition according to Claim 23, in which the vector is a virus.
25. A composition according to Claim 24, in which the virus is an adenovirus, an adeno-associated virus, a herpes virus or a retrovirus.
26. A composition according to Claim 24 or Claim 25, in which the viral vector is a replication-defective recombinant virus.
27. A composition according to Claim 26, where the virus is a replication-defective adenovirus comprising a promoter selected from the group consisting of respiratory syncytial virus promoter, cytomegalovirus promoter, adenovirus major late protein (MLP), VA1 pol III and b-actin promoters.
28. A composition according to Claim 27, wherein the vector is pAd.RSV, pAd.MLP or pAd.VA1.
29. A composition according to Claim 27, wherein the vector is Ad.RSV. α VEGF or Ad.VA1. α VEGF.
30. A composition according to any one of Claims 1 to 29, wherein the vector also comprises a polyadenylation signal sequence.
31. A composition according to Claim 30, wherein the polyadenylation signal sequence is the SV40 signal sequence.
32. A composition for treatment of a retinal disease mediated by abnormal vascularization, comprising an anti-sense nucleic acid sequence corresponding to at least a part of the sequence encoding VEGF, and optionally further comprising one or more adjuvants for increasing cellular uptake, together with a pharmaceutically-acceptable carrier.
33. (Amended) A composition according to Claim 32, comprising as adjuvant hyaluronic acid or a derivative thereof.
- 34 [33]. (Amended) A composition according to Claim 32 or Claim 33, wherein the anti-sense sequence has 100% complementarity to a corresponding region of the gene encoding VEGF.
- 35 [34]. (Amended) - A composition for short-term treatment according to Claim 32 or Claim 33, wherein the anti-sense sequence is 16 to 50 nucleotides long.
- 36 [35]. (Amended) A composition for short-term treatment according to Claim 32 or Claim 33 [34], wherein the anti-sense sequence is 16 to 22 nucleotides long.
- 37 [36]. (Amended) A composition for short-term treatment according to Claim [35] 32 or Claim 33, wherein the anti-sense sequence is 16 to 19 nucleotides long.

38 [37]. (Amended) A composition according to Claim 32 or Claim 33, wherein a modified oligonucleotide as herein defined is used, and the anti-sense sequence is 7 to 50 nucleotides long.

[38. (Amended) A composition according to any one of Claims 32 to 37 wherein the adjuvant is hyaluronic acid or a derivative thereof.]

39. (Amended) A composition for long-term treatment of a retinal disease mediated by abnormal vascularization, comprising a recombinant virus comprising an anti-sense nucleic acid sequence corresponding to at least part of the sequence encoding VEGF, together with a pharmaceutically-acceptable carrier, wherein the anti-sense sequence is between 20 nucleotides in length and the full length sequence encoding VEGF.

40. (Amended) A composition according to Claim 39, further comprising as adjuvant hyaluronic acid or a derivative thereof.

41. (Amended) A composition according to Claim 39, or Claim 40 wherein the anti-sense sequence is between 50 nucleotides long and the full length sequence of VEGF.

42 [41]. (Amended) A composition according to any one of Claims [1 to 40] 22 to 41, wherein the VEGF sequence is that of VEGF from human retinal pigment epithelial cells or choroidal endothelial cells.

43 [42]. (Amended) A composition for treatment of a retinal disease mediated by abnormal vascularization, wherein said treatment is effective for an indefinite period, comprising a virus comprising an anti-sense DNA corresponding to at least part of the sequence encoding VEGF, together with a pharmaceutically-acceptable carrier, wherein said virus is one capable of integrating the anti-sense sequence into the genome of the target cell.

44. (Amended) A composition according to Claim 43, further comprising as adjuvant hyaluronic acid or a derivative thereof.

45 [43]. (Amended) A composition according to Claim [42] 43 or Claim 44, wherein the virus is an adeno-associated virus.

46 [44]. (Amended) A composition according to [Claim 42 or] Claim 43, Claim 44, or Claim 45, wherein the anti-sense sequence is between 20 nucleotides long and the full length sequence of VEGF.

47 [45]. (Amended) A composition according to Claim 43, Claim 44, or Claim 45, wherein the anti-sense sequence is between 50 nucleotides long and the full length sequence of VEGF.

48 [46]. (Amended) A method of treatment of a retinal disease mediated by abnormal

neovascularization, comprising the step of administering an effective amount of an anti-sense nucleic acid sequence corresponding to at least part of the sequence encoding VEGF into the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization.

49. (Amended) A composition according to Claim 48, further comprising as adjuvant hyaluronic acid or a derivative thereof.

50 [47]. (Amended) A method according to Claim [46] 48 or Claim 49, wherein the anti-sense sequence is 16 to 50 nucleotides long.

51 [48]. (Amended) A method according to Claim [46] 48 or Claim 49, wherein the anti-sense sequence is 16 to 22 nucleotides long.

52 [49]. (Amended) A method according to Claim [46] 48 or Claim 49, wherein the anti-sense sequence is 16 to 19 nucleotides long.

53 [50]. (Amended) A method according to Claim [46] 48 or Claim 49, wherein a modified oligonucleotide as herein defined is used, and the anti-sense sequence is 7 to 50 nucleotides long.

54 [51]. (Amended) A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering an effective amount of a composition according to any one of Claims 22 to [45] 47 to a subject in need of such treatment.

55 [52]. (Amended) A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering a composition according to any one of Claims 39 to 42 [41] to the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization in the long term.

56 [53]. (Amended) A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering an effective amount of a composition according to Claims 42 to 47 [45] into the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization for an indefinite period.

57 [54]. (Amended) A method according to any one of Claims 48 to 56 [46 to 53], wherein the retinal disease is selected from the group consisting of age-related macular degeneration, diabetic retinopathy, branch or central retinal vein occlusion, retinopathy of prematurity, rubeosis iridis and corneal neovascularization.

58 [55]. (Amended) A method of promoting uptake of an exogenous nucleic acid sequence by a target cell, comprising the step of exposing the cell to the nucleic acid, or to a virus or vector comprising the nucleic acid, in the presence of a hyaluronic acid or a derivative thereof.